

***Pneumocystis carinii* Pneumonia in Human Immunodeficiency Virus (HIV)–Positive and HIV–Negative Immunocompromised Patients**

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For 89 human immunodeficiency virus (HIV)–positive and 32 HIV–negative immunocompromised patients who had 121 episodes of *Pneumocystis carinii* pneumonia (PCP), clinical features and changes over time were compared. HIV–infected patients characteristically had a longer duration of symptoms (23 vs. 13 days; $P < .005$); were younger (39 vs. 48 years; $P < .001$); had a higher frequency of sweating, weight loss, and thoracic pain; and had fewer admissions to the intensive care unit (16% vs. 31%; $P < .05$). In addition, they had significantly higher hemoglobin levels, lower thrombocyte counts, lower C–reactive protein values, and a higher proportion of eosinophils and lymphocytes in bronchoalveolar lavage fluid. After 1995, HIV–negative patients' mean length of stay dropped from 34 days to 16 days ($P < .005$), and their hospital mortality rate dropped from 29% to 7% ($P < .001$). HIV–positive patients with PCP differed in several aspects from those without HIV infection. Knowledge gained from experience with treatment of opportunistic infections in patients with AIDS has improved the management of PCP in patients with other immunodeficiencies.

Pneumocystis carinii was first appreciated as a human pathogen when it was causally related to pneumonia in premature, marasmic infants in European orphanages after World War II [1]. From the 1950s to the 1970s, ~100 cases of *P. carinii* pneumonia (PCP) in severely immunocompromised patients were diagnosed and reported each year in the United States [2, 3]. Cases increased markedly with the outbreak of the HIV epidemic. Since then, medical interest in PCP has focused on patients with AIDS. However, with the increasing number of patients receiving organ transplants, immunosuppressive therapy for a large variety of other diseases, and high–dose chemotherapy, PCP has become more frequent in such patients. PCP now occurs in immunocompromised patients with various underlying diseases [4–12].

Few studies have analyzed PCP in patients with AIDS as compared to those with other immunodeficiencies [13–16]. These studies mainly included patients from the 1980s. Therefore, the effect of PCP prophylaxis and, in particular, highly active antiretroviral therapy (HAART, which has dramatically changed the outcome of HIV infection in the 1990s) could not be assessed. Increasing awareness of PCP, as well as diagnostic and therapeutic progress, may have changed the picture of this disease, especially in HIV–infected patients. The present study

was performed to compare clinical features of PCP in patients with and without HIV infection. Attention was given to changes that have occurred over time.

We were confronted with an increasing number of cases of PCP involving patients without HIV infection, whereas the yearly incidence of PCP in HIV–infected patients remained stable after the introduction of effective prophylaxis for PCP and even declined when HAART became available [17–21]. The pathogenesis of PCP may be different in patients with AIDS and those with compromised immunity due to other causes [22]. In addition, it is likely that underlying diseases, as well as the awareness of the treating physicians, may have influenced the course and outcome of PCP in the 2 groups. Therefore, we analyzed data from all patients with PCP from 1983, when the first case was diagnosed in our institution, to June 1998. HIV–positive patients were compared to HIV–negative immunocompromised hosts with PCP.

Patients and Methods

The Basel University Hospital, in Basel, Switzerland, is an 800–bed facility that has averaged 230,000 patient–days per year during the past 5 years. It offers primary as well as tertiary care and is the major provider of acute medical care for the population of the city of Basel.

In patients with clinical or radiological signs of PCP, the diagnosis was made by means of fiberbronchoscopy and bronchoalveolar lavage (BAL), with use of standard techniques [23, 24]. Presumptive therapy for PCP was not administered during the observation period. From the cytological database of the Institute for Pathology (Basel), all lavages revealing *P. carinii* were screened. Available charts of all patients treated for PCP at the Department of Internal Medicine of the University Hospitals of Basel until June 1998 were selected and analyzed. Data on underlying diseases, im-

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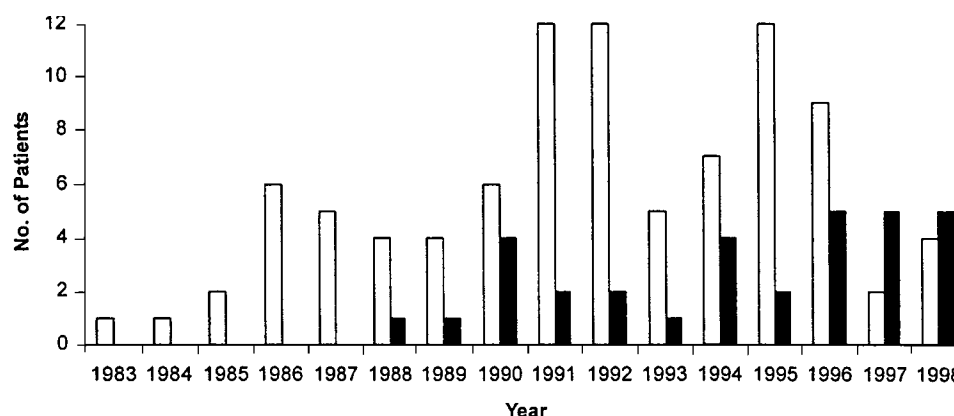


Figure 1. Incidence of *Pneumocystis carinii* pneumonia (PCP): no. of patients per year with PCP admitted to University Hospitals of Basel and included in the study. White and black columns represent HIV-positive and HIV-negative patients, respectively.

munosuppression, clinical characteristics, laboratory values, anti-pneumocystic treatment, PCP prophylaxis, outcome, and length of stay were extracted. Deaths due to any cause occurring during the hospital stay were considered in determining mortality, regardless of whether they were related to PCP.

All data were stored in a computerized database. Quantitative parameters were given as means (\pm SD) when normally distributed; otherwise, they were given as medians (minimum–maximum). Qualitative parameters were given as proportions (percentages). Differences were calculated by means of Fisher's exact test on a 2×2 table for proportions and Student's *t* test or Mann-Whitney *U* test for quantitative data. Statistical analysis was performed with the software StatView 5.0 (SAS Institute, Cary, NC).

Results

During the 16-year observation period, 132 patients fulfilled the inclusion criteria, but records were missing for 11. Therefore, 121 patients were included in this study: 89 HIV-infected and 32 HIV-negative immunocompromised patients. There was a predominance of males in both groups. Of the HIV-positive patients, 77 (87%) were male and 12 (13%) were female; of HIV-negative patients, 20 (63%) were male, 12 (38%) female.

The number of patients with PCP admitted per year is shown in figure 1. It increased among HIV-positive patients until 1991 (up to 12 patients a year) and started to decrease after 1995, when HAART became available. In the last 2.5-year period, the incidence of PCP was equal in HIV-positive and HIV-negative patients. Among the immunocompromised hosts without HIV infection, the first case was detected in 1988, and the number of cases increased to 5 per year, as shown in figure 1. During the observation period, a constant number of kidneys (53 ± 10 ; total, 910) were transplanted each year. The yearly number of bone-marrow transplantations varied from 17 in 1989 to 32 in 1998 (total, 367).

AIDS patients with PCP had a median CD4 cell count of

$34/\mu\text{L}$ (range, 0–530/ μL). Before diagnosis of PCP, 11 (12%) were in stage A of the Centers for Disease Control and Prevention's classifications for HIV infection, 41 (46%) were in stage B, and 37 (42%) were in stage C, indicating that PCP was the first AIDS-defining event in 58% of the patients. Ten (11%) received PCP prophylaxis, and 23 (26%) had received antiretroviral therapy; either monotherapy ($n = 21$), a combination of 2 nucleoside reverse transcriptase inhibitors ($n = 2$), or a triple combination including a protease inhibitor ($n = 1$).

HIV infection had been acquired by 41 (46%) of 89 patients through homosexual intercourse; by 27 (30%) of 89 through illicit iv drug use; and by 12 (13%) of 89 through heterosexual intercourse. For the remaining 9 (10%) of 89 patients, the acquisition of HIV infection was of another or unknown pattern. In all patients without HIV infection, an underlying condition impairing the immune system or a disorder treated with immunosuppressive agents was present. Immunosuppression for transplantation was the major contributing factor (table 1). The median lapse between transplantation and diagnosis of PCP was 125 days for kidney transplant recipients and 95 days for bone marrow–transplant recipients. CD4 lymphocyte counts were not routinely assessed. The median absolute lymphocyte

Table 1. Predisposing factors in HIV-negative patients with *Pneumocystis carinii* pneumonia.

Underlying disorder	No. (%) of patients
Renal transplantation	19 (59)
Bone marrow transplantation (BMT)	5 (16)
Hematologic malignancy without BMT	3 (9)
Chronic lymphatic leukemia	1
Hodgkin's disease	1
Multiple myeloma	1
Autoimmune disease	4 (13)
Sarcoidosis	2
Rheumatoid arthritis	1
Rapidly progressing glomerulonephritis	1
Idiopathic CD4 cell deficiency	1 (3)

Table 2. Clinical characteristics of patients with *Pneumocystis carinii* pneumonia (PCP).

Clinical characteristic	HIV-positive (n = 89)	HIV-negative (n = 32)	P
Age (y)	39 ± 9.9	48 ± 13	<.001 ^a
Duration of symptoms ^b (d)	23 ± 17	13 ± 12	<.005 ^a
Systolic blood pressure (mm Hg)	115 ± 15	125 ± 20	<.05 ^a
Diastolic blood pressure (mm Hg)	71 ± 11	73 ± 12	.46
Tachycardia, >100/min	24 (27)	8 (25)	.99
PCP prophylaxis	10 (11)	0 (0)	—
Cough	60 (67)	18 (56)	.68
Dyspnea	49 (55)	20 (63)	.54
Expectoration	30 (39)	8 (25)	.51
Tachypnea, >15/min	30 (34)	7 (22)	.64
Thoracic pain	25 (28)	3 (9)	<.05 ^c
Hemoptysis	3 (4)	3 (9)	.19
Fever >38°C	56 (62)	20 (63)	.99
Weakness	51 (57)	15 (47)	.41
Loss of appetite	42 (47)	12 (38)	.41
Sweating	39 (44)	6 (19)	<.05 ^c
Weight loss	38 (43)	4 (13)	<.01 ^c
Cachexia	32 (36)	3 (9)	<.01 ^c

NOTE. Data are no (%) of patients or mean ± SD.

^a Unpaired Student's *t* test, two-tailed.^b Until diagnosis of PCP.^c Fisher's exact test.

count was 380/ μ L (range, 0–3370/ μ L). None of these patients received PCP prophylaxis.

HIV-infected patients were younger than HIV-negative patients (mean age, 39 vs. 48 years; $P < .001$), and the time from the onset of symptoms until diagnosis of PCP was longer (23 vs. 13 days; $P < .005$). Main features of PCP, such as pulmonary symptoms, fever, and weakness, occurred at similar frequencies in both groups. In contrast, significant differences were found with regard to thoracic pain, sweating, weight loss, and cachexia, all of which occurred more frequently in HIV-infected patients (table 2).

There was no difference in the gas exchange values between the 2 groups. In contrast, HIV-positive patients had higher values for hemoglobin, lower thrombocyte counts, and lower values for C-reactive protein (table 3).

Cytological analyses of BAL specimens showed >3% neutrophils in 51 (74%) of 69 HIV-positive patients and 18 (67%) of 27 HIV-negative patients ($P > .05$). Eosinophils were found significantly more often in the BAL specimens from HIV-positive patients (23 [33%] of 69 vs. 2 [7%] of 27; $P < .01$). Similarly, a finding of >15% lymphocytes was more frequent for HIV-positive patients (41 [59%] of 69 vs. 13 [48%] of 27; $P < .05$).

The length of hospital stay was significantly shorter for HIV-positive patients than for HIV-negative patients in the period of 1983–1995 (table 4). It dropped 2.1-fold ($P < .005$) from the earlier to the later period for HIV-negative patients, whereas it remained similar in both periods for HIV-infected patients. For the whole observation period, the length of stay did not differ in the 2 groups. However, a larger proportion of the HIV-negative cohort was admitted to the intensive care unit (ICU)

and required mechanical ventilation (table 4). There was a trend toward a higher hospital mortality rate in this group, but mortality dropped 4.1-fold ($P < .001$) to reach 7% in the period of 1996–1998 (figure 2).

The antimicrobial agents administered to HIV-positive and HIV-negative patients (including switches in therapy) were co-trimoxazole (62% vs. 72%), dapsone/trimethoprim (28% vs. 25%), pentamidine (11% vs. 16%), and atovaquone (1.1% vs. 38%; $P < .001$).

Discussion

In this 16-year study of 121 patients with PCP, we compared the clinical characteristics of patients with and without HIV infection. Previous studies were smaller [13–16] and were performed in the era before the availability of antiretroviral therapy and the introduction of primary PCP prophylaxis for HIV-infected patients [14–16]. In our study, the main differences in the presentation of PCP between HIV-positive and HIV-negative patients were as follows: HIV-positive patients were (1) younger than HIV-negative patients, (2) had a longer duration of symptoms, (3) a higher frequency of general symptoms (sweating, weight loss, cachexia), and (4) a higher frequency of thoracic pain. In addition, HIV-infected patients with PCP had higher hemoglobin values, lower thrombocyte counts, and lower C-reactive protein values. Hospital mortality was similar in both groups. However, a greater proportion of HIV-negative patients was treated in the ICU and mechanically ventilated.

In 3 published studies, the duration of symptoms in HIV-infected patients was consistently longer than for HIV-negative patients [13–15]. Mortality, however, was higher [15], lower [13], or equal at a high level [14].

The higher proportion of HIV-negative patients admitted to the ICU and requiring mechanical ventilation, as well as the somewhat higher overall mortality, suggests that HIV-negative patients with PCP had a higher rate of comorbidity than did HIV-infected patients. The younger age of patients with AIDS may also have contributed to their lesser need for an ICU stay and mechanical ventilation. A third explanation is the higher degree of suspicion of a diagnosis of PCP for HIV-infected

Table 3. Laboratory values at diagnosis of PCP for HIV-positive and HIV-negative patients.

Parameter	HIV-positive	HIV-negative	P ^a
Arterial partial pressure of CO ₂ (kPa)	4.3 ± 0.7	4.6 ± 0.9	.13
Arterial partial pressure of O ₂ (kPa)	9.1 ± 3.6	9.2 ± 3.8	.91
Arterial pH	7.43 ± 0.07	7.43 ± 0.11	.91
Hemoglobin (g/dL)	11.6 ± 2.2	9.52 ± 1.7	<.01
Leukocytes ($\times 10^9$ /L)	5.2 ± 2.1	6.4 ± 4.0	.11
Thrombocytes ($\times 10^9$ /L)	212 ± 84.8	262 ± 148	<.05
Lactate dehydrogenase (mmol/L)	930 ± 668	634 ± 358	.11
C-reactive protein (mg/L)	66 ± 53.6	123 ± 114	<.01

NOTE. Data are mean ± SD.

^a Unpaired Student's *t* test, two-tailed.

Table 4. Length of hospital stay (LOS), intensive care unit (ICU) data, and outcome for HIV-positive and HIV-negative patients.

Parameter	HIV-positive (n = 89)	HIV-negative (n = 32)	P
LOS, mean no. of days (range)			
1983–1998	20.5 (2–88)	22 (5–122)	.31 ^a
1983–1995	19.5 (2–88)	34 (5–122)	<.01 ^a
1996–1998	14.5 (2–50)	16 (4–69)	.95 ^a
In ICU			
Patients	14 (16)	11 (31)	<.05 ^b
Mean no. of days (range)	6.5 (1–18)	13 (2–58)	.65 ^a
Mechanical ventilation	8 (16)	7 (64)	<.05 ^b
Deaths	3 (38)	4 (50)	.3 ^b
Deaths in hospital	10 (11)	5 (19)	.54 ^b

NOTE. Data are no. (%) of patients, except as noted.

^a Mann-Whitney U test.^b Fisher's exact test.

patients, resulting in diagnosis and antimicrobial therapy at a less advanced stage of pneumonia.

Indeed, despite a constant incidence of PCP of 10–14 cases a year since 1990, the number of BALs performed at our hospital for the diagnosis of PCP in HIV-infected patients increased from 55 in 1990 to 79 in 1995. This suggests increasing awareness of PCP on the part of emergency department physicians. Compared to data for the period of 1983–1995, PCP-associated mortality in HIV-negative patients, as well as the length of hospital stay, sharply decreased to reach those for HIV-infected patients (table 4; figure 2).

In contrast, mortality and length of hospital stay for HIV-infected patients did not significantly change over time, nor did the yearly number of transplantations increase. This suggests that the focus on HIV infection, in association with increasing experience in the treatment of opportunistic infections, has improved the management of PCP in patients with other types of immunosuppression.

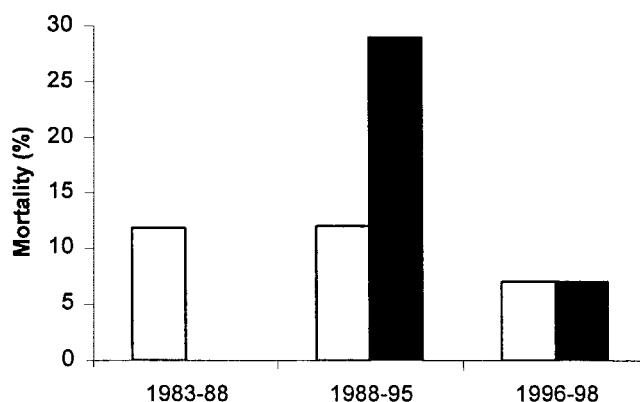


Figure 2. Mortality among patients admitted with *Pneumocystis carinii* pneumonia (PCP). White and black columns represent HIV-positive and HIV-negative patients, respectively. There was trend toward higher hospital mortality among HIV-negative patients until 1996 ($P = .13$, Fisher's exact test).

Eosinophilia and lymphocytosis in the BAL specimens from HIV-infected patients with PCP have been described elsewhere [25]. These findings were absent in the group of immunosuppressed HIV-negative patients, probably because of their immunosuppressive therapy with corticosteroids.

PCP prophylaxis is well established for HIV-infected patients and has proved to be effective [17–20]. Of the HIV-infected patients who developed PCP, only 11% were receiving prophylaxis. This is in contrast to the overall data from the Swiss HIV Cohort participants; >85% of them, for whom at least 2 CD4 cell counts were $<200/\mu\text{L}$, received PCP prophylaxis (personal communication, Dr. M. Rickenbach, Swiss HIV Cohort Study Data Center, Lausanne, Switzerland). This indicates that failure of prophylaxis is rather infrequent, and PCP occurred mainly in HIV-infected individuals at risk who did not receive PCP prophylaxis.

The introduction of HAART in Switzerland has led to a significant reduction in progression to AIDS in HIV-infected patients [21]. This has led in turn to a marked decrease of admissions for PCP in our hospital since 1995. In our study, only 1 patient admitted for PCP was receiving HAART.

PCP prophylaxis has also proved to be effective in various groups of HIV-negative immunosuppressed patients [26–29]. None of the HIV-negative patients included in this study was receiving prophylaxis. Since PCP-related mortality is still high, further efforts are needed to assess HIV-negative immunocompromised patients who may benefit from PCP prophylaxis. In a recent observational study, it was suggested that PCP prophylaxis should be given to all solid organ transplant recipients for at least 1 year. In patients with recurrent or chronic rejection and in lung transplant recipients, it should be continued during risk and indefinitely, respectively [30]. In another observational study on heart transplant recipients, PCP recurrence was not observed when the CD4 cell count was $>150/\mu\text{L}$ [31].

In conclusion, HIV-infected patients with PCP differ in several clinical and laboratory aspects from those with PCP but without HIV infection. If PCP prophylaxis were used not only for HIV-infected patients at risk but also for transplant patients with absolute lymphocyte counts $<500/\mu\text{L}$ and within 180 days after transplantation, the incidence of PCP would probably markedly drop.

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